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A priori free spectral unmixing with periodic absorbance changes: Application for auto-calibrated intraoperative functional brain mapping

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1. Statistical parametric mapping

To identify the functional brain areas from the computed contrasts, the statistical parametric mapping (SPM) technique [1] was implemented. This technique was introduced by Karl Friston to process fMRI data. This method was also adapted for functional near infrared applications [2, 3]. We adapted this methodology for intraoperative functional RGB imaging. The basic idea was to test for each camera pixel the linear association between measured contrasts and a theoretical contrast that describes the patient hemodynamic response to a physiological stimulus. This theoretical contrast was obtained by convolving the hemodynamic impulse response function [4] to the window function that represents the patients physiological stimulus. This curve is called expected hemodynamic response in the rest of the manuscript. A general linear model was implemented to evaluate the linear association between measured and expected responses:

$$Y_c = X_c \beta_c + e. \tag{1}$$

Y_c is the matrix of the contrast c of dimension $T \times N$ (with T the number of frames and N the number of pixels). The contrast c is either ΔC_{HbO_2} or ΔC_{Hb}. X_c is the design matrix of the contrast c of dimension $T \times S$. S designates the number of patient's physiological conditions (for example: rest and activity). The matrix X_c contains the theoretical response for each physiological condition: zero values for patient's rest and the expected response of the contrast c for patient's activity.

When the contrast c was ΔC_{HbO_2}, the expected response was obtained by convolving the hemodynamic impulse response function [4] to the window function representing the experimental paradigm (rest: 0 and activity: 1). When the contrast c was ΔC_{Hb}, the hemodynamic response computed for ΔC_{HbO_2} was multiplied by -1. β_c is a matrix of dimension $S \times N$ that contains the parameters of the general linear model for the contrast c. These parameters explain the association of each pixel to the physiological conditions expressed in the design matrix. e is a matrix of dimension $T \times N$ that represents the errors of the model. The values of the matrix e are supposed to be independent errors consisting of Gaussian noise of zero mean and variance matrix $\sum_e = \sigma^2 \times I$ (σ^2 is the variance in e and I is the identity matrix). Under these assumptions, the matrix β_c can be estimated with the Gauss-Markov theorem:

$$\beta_c = (X_c^t X_c)^+ X_c^t Y_c. \tag{2}$$

^{t} is the transposition operator. The matrix t_{stat} of dimension $N \times 1$ represents the matrix of t statistics for testing the null hypothesis (no cerebral activation):

$$t_{stat} = \frac{cv^t \beta_c}{\sqrt{\sigma^2 cv^t (X_c^t X_c)^+ cv}}. \tag{3}$$

In this equation, cv is the contrast vector used to extract the parameters of the β_c matrix associated to one of the patient's physiological conditions (one condition among the S ones expressed in the design matrix). For example, if two conditions are defined (rest and activity), $cv = [1 \quad 0]$ aims to extract parameters associated to rest, and $cv = [0 \quad 1]$ those related to patient's activity. In this study, we have chosen $cv = [0 \quad 1]$.

1.1. Random field theory

The t_{stat} matrix can be used to compute statistical inferences, it means to indicate if a pixel is associated or not with a functional brain area. In a multiple statistical comparison problem, the definition of a statistical threshold is most often calculated with the Bonferroni correction method. However in our study, this method is too restrictive due to the high image definition. To overcome this issue, the random field theory (RFT) is commonly used in fMRI and fNIRS studies [2, 5, 6]. This method allows to threshold statistical parametric maps at 5% statistical significance level with a correction for multiple comparisons (family-wise error) at the pixel level.

RFT is composed of several steps. First, the t_{stats} matrix is converted into z statistics (Z_{stats}). Then the Z_{stats} matrix is smoothed with a Gaussian kernel. The full width at half maximum (FWHM) of this kernel aims to define the number of *resels* (resolution elements) [7]. For example, if a 100×100 pixels matrix is convoled with a Gaussian kernel of FWHM$= 5 \times 5$ pixels, the number of resels is $20 \times 20 = 400$. The Euler characteristic (EC) is then computed for a Z_{stats} threshold (Z_{th}). The EC aims to estimate the number of clusters obtained in an image that contains randomly distributed values after a thresholding operation. For high threshold values, the RFT indicates that: $P[EC(Z_{th}) \geq 1] = E[EC(Z_{th})]$ (the probability that at least one cluster is detected in the image after thresholding the image at Z_{th} is equal to the average value of $EC(Z_{th})$). For an image of z statistics image smoothed with a Gaussian kernel and composed of r_{tot} *resels*, the mean of EC computed for a threshold value Z_{th} is:

$$E[EC(Z_{th})] = (2\pi)^{-3/2} (4 \ln(2)) \, r_{tot} \, Z_{th} \exp\left(-Z_{th}^2/2\right). \tag{4}$$

The threshold value Z_{th} was calculated such that $E[EC(Z_{th})] = 0.05$. In other words, Z_{th} was calculated such that a cluster (a functional brain area) is identified in the Z_{stats} matrix with the rejection of the null hypothesis at 5% significance level (there is no cerebral activity, *i.e.* measured and expected hemodynamic responses do not correspond).

1.2. Automatic thresholding procedure

In some cases, measured and expected hemodynamic responses did not correspond because the actual hemodynamic impulse response in the patient's tissue was different from the one used in this paper (standard hemodynamic response function used in fMRI clinical studies). This leads to a lack of detection of functional brain areas due to a too high threshold of the Z_{stat} matrix using RFT. In these cases, we applied an automatic thresholding procedure on Z_{stat} maps: functional brain areas were identified as portions of patient's brain where the $Z_{stat} > \mu(Z_{stat}) + 0.75\sigma(Z_{stat})$ [8], with μ and σ the mean and standard deviation functions, respectively. In intraoperative optical imaging of intrinsic signals studies, an automatic thresholding procedure is often used to delineate activation maps [9–12]. It should be noted that the method used to calculate the functional maps was different in these studies. The authors applied an automatic thresholding procedure on the relative intensity change maps to produce topological maps of brain activity.

The binary image obtained after the thresholding operations is indicated SPM_c in the rest of the paper.

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